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Highly Enantioselective Synthesis of (*S*)-α-Alkyl-α,*β*-diaminopropionic Acids via Asymmetric Phase-Transfer Catalytic Alkylation of 2-Phenyl-2-imidazoline-4-carboxylic Acid *tert*-Butyl Esters

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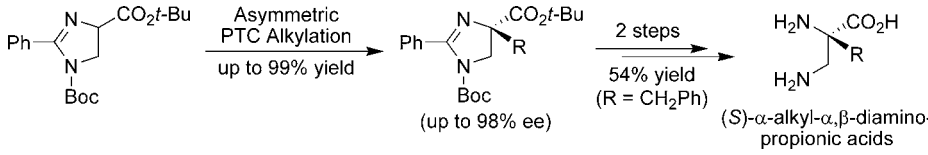
ABSTRACT



An efficient enantioselective synthetic method for (*S*)-α-alkyl-α,*β*-diaminopropionic acid is reported. The asymmetric phase-transfer catalytic alkylation of *N*(1)-Boc-2-phenyl-2-imidazoline-4-carboxylic acid *tert* -butyl ester in the presence of chiral quaternary ammonium catalyst gave the corresponding alkylated products (93−98% ee) which could be transformed to enantioenriched α-alkyl-α,*β*-diaminopropionic acids.

α,*β*-Diamino acids **1** have been regarded as attractive synthetic targets in view of their various biological activities. As nonnatural amino acids, they not only resist proteolysis, but also form stabilized and specific conformations of the peptides containing them.[1,2] Chiral α,*β*-diaminocarbonyl moieties can be found in several, naturally occurring cyclopeptidic antibiotics, such as bleomycin, capreomycin, viomycin, and tuberactiomycin. Also, several imidazoline compounds derived from chiral α-alkyl-α,*β*-diamino acids have exhibited antitumor activity.[3] Furthermore, optically active α-alkyl-α,*β*-diamino acids can be easily cyclized to *β*-lactams, which give rise to new, valuable *β*-lactam antibiotics.[4]

A number of enantioselective synthetic methods for α-alkyl-α,*β*-diaminopropionic acids have been reported thus far,[5] with most based on the diastereoselective α-alkylation of chiral glycine equivalents,[5b] on the α-amination of chiral α-cyanoesters,[5c,d] and on the chiral asparagines.[5d] Since most of the reported methods employ chiral substrates or chiral

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(1) For a comprehensive review on synthetic approach and biological significance of α,*β*-diamino acids, see: Viso, A.; Fernández de la Pradilla, R.; Garcia, A.; Flores, A. *Chem. Rev.* **2005**, *105*, 3167.

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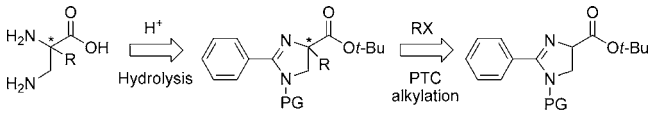
auxiliaries, their applications in industry for large scale production might prove difficult. In this letter, we report a new efficient synthesis of (*S*)-α-alkyl-α,*β*-diaminopropionic acids via asymmetric phase-transfer catalytic α-alkylation of imidazoline-4-carboxylates which could be applied to industrial process.[6,7]

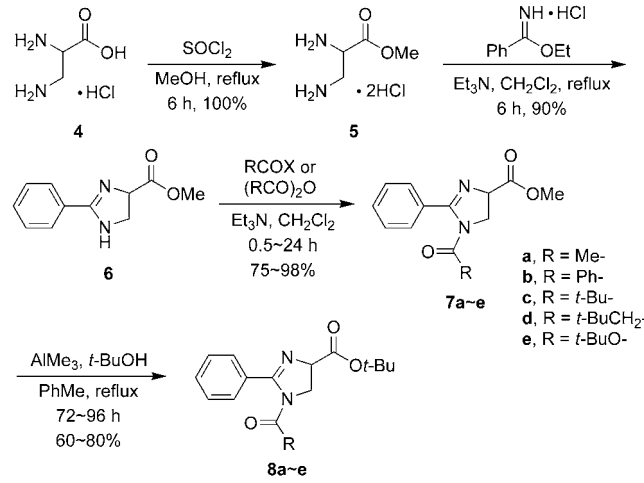
Very recently, we reported a series of new synthetic methods for optically active α-alkylserines and α-alkylcysteines by the catalytic enantioselective α-alkylation of *tert*-butyl 2-phenyloxazoline-4-carboxylate and *tert*-butyl 2-phenylthiazoline-4-carboxylate under phase-transfer conditions, respectively.[8] These works demonstrated that the phase-transfer catalytic conditions are very efficient for the α-alkylation of the oxazoline-4-carboxylate and the thiazoline-4-carboxylate systems. On the basis of our previous results, we attempted to apply the phase-transfer catalytic alkylation of imidazoline-4-carboxylate system **3** for the enantioselective synthesis of chiral α-alkyl-α,*β*-diaminopropionic acids **1** (Scheme 1).

Scheme 1. Synthetic Strategy for Optically Active α-Alkyl-α,*β*-diaminopropionic Acids via Asymmetric Phase-Transfer Catalysis

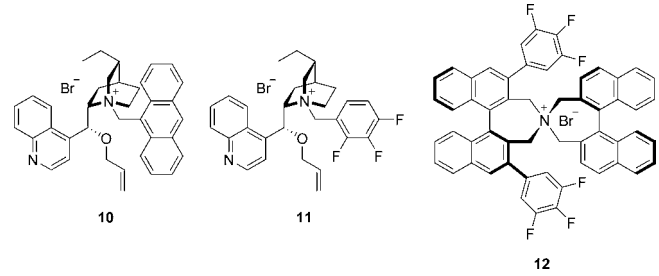


First, the substrate, *N*(1)-protected-2-phenyl-2-imidazoline-4-carboxylic acid *tert*-butyl ester **3**, was prepared from commercially available α,*β*-diaminopropionic acid (**4**) in four steps. The methyl esterification of **4** using thionyl chloride in methanol, followed by coupling with ethyl benzimidate, afforded methyl 2-phenyl-2-imidazoline-4-carboxylate (**6**). Before the transesterification of **6** to the corresponding *tert*-butyl ester, it was necessary to protect the *N*(1)-H of the imidazoline. Five kinds of *N*(1)-acyl protections with acid chlorides or acid anhydrides in the presence of triethylamine gave *N*(1)-acylimidazolines **7a**−**e**, which were then converted to the corresponding *tert*-butyl esters **8a**−**e** by transesterification using $AlMe_3$ and *tert*-butanol in toluene[8b] (Scheme 2).

Scheme 2. Preparation of 2-Phenyl-2-imidazoline-4-carboxylates



For asymmetric phase-transfer catalytic alkylation, we adapted our previous reaction conditions.[8] phase-transfer catalytic benzylations of **8a**−**8e** were performed using 5.0 mol % of the representative phase-transfer catalysts (PTCs)[9] (**10**,[9a] **11**,[9b] **12**[9c]) along with benzyl bromide (5.0 equiv) and solid KOH (5.0 equiv) in toluene at 0 °C for 1.5−16 h.



As shown in Table 1, the binaphthalene-derived PTC **12** (entry 3, 98% ee) showed the best enantioselectivity, while the cinchona PTCs **10** (entry 1, 72% ee) and **11** (entry 2, 75% ee) afforded low and moderate enantioselectivity, respectively. The chemical yields and enantioselectivities were variable depending on the *N*(1)-protective group of the imidazoline substrates. In terms of enantioselectivity, the *tert*-butyl-possessing acyl groups (**8e**, **8c**, **8d**) gave very high enantioselectivities (entry 3, 98% ee; entry 6, 98% ee; entry 7, 95% ee). The bulky *tert*-butyl groups might play an

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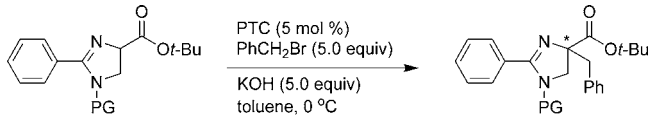
Table 1. Screening of Substrate and PTC



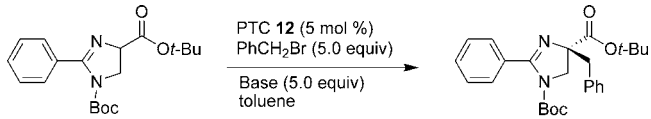
8a~8e 9aC~9eC

entry	8	PTC	time (h)	yield (%)[a]	ee (%)[b]
1	**8e**	**10**	4	49	72
2	**8e**	**11**	4.5	43	75
3	**8e**	**12**	16	95	98
4	**8a**	**12**	1.5	70	93
5	**8b**	**12**	2	92	89
6	**8c**	**12**	6	77	98
7	**8d**	**12**	5	79	95

[a] Isolated yields. [b] Enantiomeric excess was determined by HPLC analysis of **9C** using a chiral column (Chiralcel AD or OD) with hexanes/2-propanol as the eluent.

integral role in the high enantioselectivities. Regarding chemical yields, aliphatic acyl groups (entries 4, 6, and 7) showed relatively lower chemical yields compared to those of the benzoyl and Boc groups (entries 3 and 5). The Boc group afforded the best results in both chemical yield and enantioselectivity. Reaction conditions were optimized with the best substrate (**8e**), by varying base and reaction temperature (Table 2). Generally, high enantioselectivities

Table 2. Optimization of Reaction Conditions



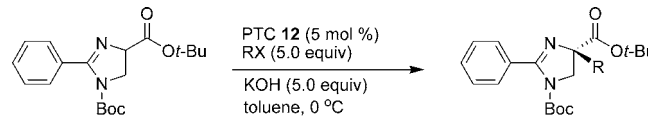
8e 9eC

entry	base	temp (°C)	time (h)	yield (%)[a]	ee (%)[b] config.
1	KOH	rt	3.5	83	95 (*S*)[d]
2	KOH	0	16	95	98 (*S*)
3	KOH	−20	24	91	96 (*S*)
4[c]	KOH	0	24	46	79 (*S*)
5	50% KOH	0	24	79	98 (*S*)
6	CsOH	0	4	88	97 (*S*)

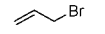
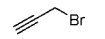
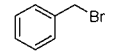
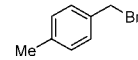
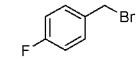
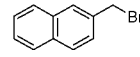
[a] Isolated yields. [b] Enantiomeric excess was determined by HPLC analysis of **9eC** using a chiral column (Chiralcel OD) with hexanes/2-propanol as the eluent. [c] 2.5 mol % of PTC **12** was used. [d] Absolute configuration was assigned by comparison of the specific optical rotation value of the α-benzyl-α,*β*-diaminopropionic acid (**1C**) prepared by hydrolysis of **9eC** with the literature value.[5d]

were observed regardless of the base conditions, but solid KOH gave the highest chemical yield (entry 2, 95%; entry 5, 79%; entry 6, 88%). Reaction temperature seemed insensitive to enantioselectivity, but the best chemical yield was observed at 0 °C (entry 2, 95%). Notably, use of less catalyst **12** decreased both chemical yield and enantioselectivity (entry 4, 46%, 79% ee). Substrate **8e** was chosen for further investigation for scope and limitation in enantioselective phase-transfer catalytic alkylation with various alkyl halides under optimal reaction conditions (entry 2 in Table 2). As shown in Table 3, very high chemical yields (87−99%) and enantioselectivities (93−98% ee) were observed for allylic, propargylic, and benzylic halides.[10]

Table 3. Enantioselective Phase-Transfer Alkylation of **8e** with Various Alkyl Halides in the Presence of **12**



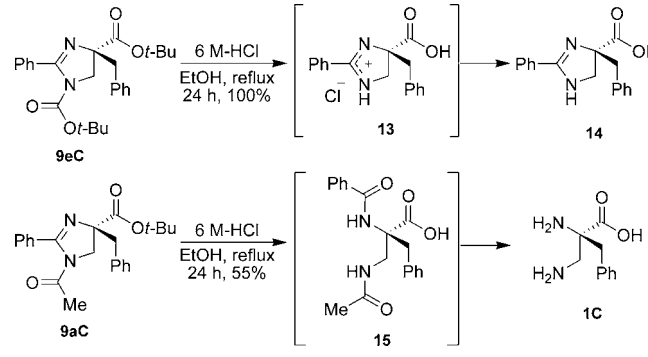
8e 9e

entry	RX	9e	time (h)	yield (%)[a]	ee (%)[b] config.[c]
1		**9eA**	3	90	95 (*S*)[d]
2		**9eB**	8	99	94 (*S*)
3		**9eC**	16	95	98 (*S*)
4		**9eD**	24	93	95 (*S*)
5		**9eE**	15	98	93 (*S*)
6		**9eF**	24	87	98 (*S*)

[a] Isolated yields. [b] Enantiomeric excess was determined by HPLC analysis of **9e** using a chiral column (Chiralcel AD or OD) with hexanes/2-propanol as eluents. [c] Absolute configuration was assigned by the comparison of the specific optical rotation value of the α-benzyl-α,*β*-diaminopropionic acid prepared by hydrolysis of **9eC** with the literature value;[5d] other absolute configurations were tentatively assigned as *S* based on the absolute configuration of **9eC**.

Hydrolysis of **9eC** (98% ee) with 6.0 M HCl was performed in order to generate α-benzyl-α,*β*-diaminopropionic acid (**1C**), interestingly, however, only the *tert*-butyl group was removed (Scheme 3). Previous results on the

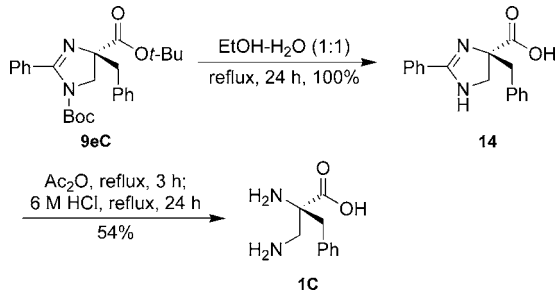
Scheme 3. Effect of *N*(1)-Substituent on the Acidic Hydrolysis of the *tert*-Butyl 2-Phenyl-2-imidazoline Carboxylates in **9eC** and **9aC**



hydrolysis of the imidazoline group of *iso*-amarine revealed that *N*(1)-acetylation should precede before the hydrolysis

of the imidazoline moiety because the protonated form **13** in acidic media is quite resistant to hydrolysis.[11] Indeed, the hydrolysis of **9aC** (93% ee) under 6.0 M HCl in ethanol readily provided **1C**, which was in accord with previous results (Scheme 4).

Scheme 4. Preparation of α-Benzyl-α,β-diaminopropionic Acid



Finally, liberation of α-benzyl-α,β-diaminopropionic acids (**1C**) from **9eC** was accomplished by a two-step sequence; (1) Removal of both *N*(1)-Boc and *tert*-butyl ester in **9eC** in refluxing EtOH-H_2O (volume ratio = 1:1) affording **14** quantitatively.[11d] (2) *N*(1)-Acetylation of **14** with acetic anhydride followed by hydrolysis with 6.0 M HCl[11e] providing (*S*)-**1C** in 54% yield {$[\alpha]_D^{25} = 12.06$ (*c* 1.0, H_2O); $[\alpha]_D^{25} = 9.2$ (*c* 0.8, H_2O)[5e]}. To the best of our knowledge, this is the first catalytic synthetic method for α-alkyl-α,β-diaminopropionic acid with very high enantioselectivities as well as high chemical yields.

In conclusion, an efficient synthetic methodology for optically active α-alkyl-α,β-diaminopropionic acid, by the asymmetric phase-transfer catalytic alkylation of *N*(1)-Boc-2-phenyl-2-imidazoline-4-carboxylic acid *tert*-butyl ester (**8e**) was developed. The facile preparation of the substrate, high enantioselectivity, and mild asymmetric alkylation conditions make this method a practical route for the preparation of versatile synthetic intermediates, (*S*)-α-alkyl-α,β-diaminopropionic acids, which can be applied to the synthesis of biologically active β-lactams, peptidomimetics, and imidazoline natural products.

Acknowledgment. This work was supported by the SRC/ERC program of MOST/KOSEF (R11-2007-107-02001-0).

Supporting Information Available: Representative experimental procedures, as well as spectroscopic characterizations of all new compounds are provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) In the cases of less reactive, aliphatic alkyl halides, the reaction rates remarkably slowed down, so that the desired products were obtained in less than 5% chemical yields even after 48 h stirring.

(11) (a) Williams, O. F.; Bailar, J. C., Jr. *J. Am. Chem. Soc.* **1959**, *81*, 4464. (b) Saigo, K.; Kubota, N.; Takebayashi, S.; Hasegawa, M. *Bull. Chem. Soc. Jpn.* **1986**, *59*, 931. (c) Corey, E. J.; Kühnle, F. N. M. *Tetrahedron Lett.* **1997**, *38*, 8631. (d) Mitchell, J. M.; Finney, N. S. *Tetrahedron Lett.* **2000**, *41*, 8431. (e) Braddock, D. C.; Hermitage, S. A.; Redmond, J. M.; White, A. J. P. *Tetrahedron: Asymmetry* **2006**, *17*, 2935.